

GROWTH REGULATION OF ENDOCYTOSIS IN CULTURED VASCULAR CELLS
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Endocytosis is involved in the metabolism of blood-borne macromolecules by both vascular endothelium and smooth muscle cells (SMC). Intimal SMC proliferation is a prominent feature of atherogenesis and therefore the interactions between the cell cycle, growth factors and endocytosis are relevant to this disease process. Manipulation of the growth of smooth muscle cells in culture by platelet-derived growth factor (PDGF), fibroblast growth factor (FGF) and epidermal growth factor (EGF) has demonstrated a coupling between endocytic volume (fluid endocytosis), endocytosis of low density lipoproteins (LDL) and growth regulation. Fluid endocytosis rate increased up to 10 fold per responding cell early in the cell cycle and continued elevated through S phase before declining. The magnitude of the effect was proportional to the fraction of cells entering the cycle, and when density-dependent inhibition of growth occurred, it was accompanied by density-dependent inhibition of fluid endocytosis rate. In addition to these changes in rate of fluid endocytosis, we also studied the high affinity binding, endocytosis and degradation of LDL. PDGF and FGF stimulated LDL binding by up to 300% and this also resulted in enhanced LDL degradation. Removal of growth factor after initiation of the cell cycle, however, abolished the response, suggesting that the continued presence of growth factor was required for enhanced LDL binding.

A direct relationship between fluid endocytosis and cell growth was also measured in cultured endothelium, but exposure of confluent endothelium to PDGF or FGF resulted in increased binding of LDL without a growth response.

These results, together with the failure to enhance binding of LDL to cycling SMC after removal of mitogen, suggest that growth factor stimulation of LDL binding and its consequences may be uncoupled from cell growth even though the common carrier for internalisation (endocytic vesicle volume) is closely related to the cell cycle.

ARTERIAL INJURY ALTERS METABOLISM OF THE ARTERIAL WALL.
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Results of our previous experiments indicate that following de-endothelialization aortic intima was thicker and contained more lipid in re-endothelialized (RA) and not de-endothelialized areas (DA) as we anticipated. Chemical analysis revealed that, in rabbits fed lipid-poor diets, there was 2 to 3 times as much cholesteryl ester (CE) in RA as compared to DA or uninjured aortas. In hypercholesterolemic rabbits, aortic total cholesterol content correlated with serum cholesterol concentration in RA but not DA. Taken together, these findings suggest that aortic cholesterol (CH) and CE accumulation are not simply a result of increased filtration of lipoproteins into the de-endothelialized aorta but may result from altered metabolism of the arterial wall. Previous findings showing increased glycosaminoglycan (GAG) accumulation in RA supported this concept of altered metabolism and suggest that these GAGs may sequester lipoproteins. Recent experiments indicate that: 1) CE synthetic and hydrolytic activity as well as activities of several marker enzymes were increased in injured aortas, 2) CE hydrolytic activity was relatively greater in DA as compared to RA, 3) Neointimal smooth muscle cells (SMC) in DA synthesized increased quantities of PGI₂ and that PGI₂ increased CE hydrolase activity of SMC and 4) RA accumulate more ¹²⁵I-apo-B-lipoproteins than adjacent DA. In conclusion, results indicate that RA accumulate more CE rich apo-B-lipoproteins and have decreased ability to degrade CE. This may, at least in part, account for the increased CH and CE accumulation in RA. Further, the findings suggest that arterial injury alters arterial wall metabolism and that interactions between neointimal smooth muscle cells and endothelial cells may modify these metabolic changes.